Non-Infectious Causes of Fever

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Mimics:

- Many non-infectious conditions masquerade as infections.
- Typically these are conditions with fever as a hallmark…..
- Or a syndrome that looks like a common infection, such as cellulitis, pneumonia, infectious diarrhea, etc.

2011 exam blueprint:

Primary Content Areas	Relative Percentage
Bacteria	16%
Viruses and prions	7%
Mycobacteria	5%
Parasites	5%
Fungi	4%
Rickettsia and chlamydia	3%
HIV	15%
Surgical consultations and critical care medicine	8%
Immunologic diseases (other than AIDS), and vaccines	4%
Infections in transplant patients	5%
Antimicrobial therapy	9%
Epidemiology, infection control, and bioterrorism	5%
Sexually transmitted diseases	3%
General (general internal medicine and ethics)	**10%**
Total	100%

Test taking tip:

- Look for “buzz words” and associations.
- For example:

  I say, “rabbit.”

  You say……

  tularemia.

I say, “leech.”
You say……

Aeromonas.

I say, “cirrhosis and oysters.”
You say……

Vibrio vulnificus.

Use same strategy for non-infectious conditions.

My plan:

- You are all internists.
- Thus, I won't go into details about each medical condition.
- But rather, I shall use cases to illustrate the kinds of questions you would be likely to find on the Board exam.

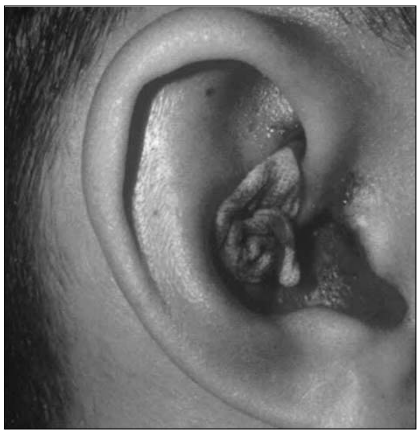
Case # 1:

- A 42-year-old man is seen for his third episode of cellulitis of the external ear. Two previous episodes involving the same ear, 2 and 5 months ago, seemed to respond very slowly to antibiotics. He has a several year history of chronic nasal stuffiness and had an episode of knee arthritis in the past year, but is otherwise well.

Case # 1:

- Exam: Afebrile. His right auricle is inflamed and tender. The ear lobe is spared. There is no regional adenopathy. He has a saddle-nose deformity; the nasal mucosa is normal. The rest of the exam is unremarkable.
- Labs: Mild, normocytic, normochromic anemia; other routine labs are normal.

Case # 1:



Question:

- The most likely diagnosis is?
  A. Invasive external otitis
  B. Leprosy
  C. Wegener's granulomatosis
  D. Relapsing polychondritis
  E. Recurrent streptococcal cellulitis

Relapsing Polychondritis:

- Immune-mediated condition associated with inflammation of cartilaginous structures, particularly ears, nose, eyes, joints, and respiratory tract.
- Clinical diagnosis.

Relapsing Polychondritis:

- Buzz words and associations:
  recurrent “cellulitis” (cartilage inflammation) and saddle-nose

Other clues:
nasal stuffiness with normal mucosa, arthritis, sparing of ear lobe, no regional adenopathy

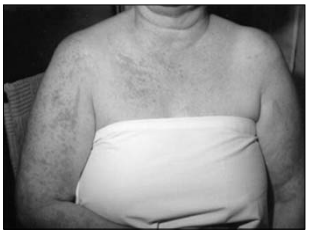
Saddle-nose Deformity:

Lepromatous leprosy
Syphilis
Wegener’s
Relapsing polychondritis

Case # 2:

- A 39-year-old woman is seen on day 4 of hospitalization for high fever and leukocytosis. The fever had been present for 3 and ½ weeks and was accompanied by severe arthralgias of the knees, wrists and ankles as well as myalgias. A severe sore throat was present during the first week of the illness.

Case # 2:



- Exams: Daily fever with T_{max} 104.2F. On two occasions an evanescent, salmon-colored, maculopapular rash was noted on the trunk and extremities, most prominently under the breasts and in the area of the waistband of her underwear. Tender cervical nodes were noted and the spleen was enlarged. Both wrists were tender.

Case # 2:

- Labs:
  Hb 11.8 (normocytic normochromic);
  Ferritin 3600 ng/ml (nl 40-200);
  WBC 32,200 (89% neutrophils);
  Sed. rate and CRP 5x normal;
  AST and ALT 3x normal; UA normal;
  Chest x-ray normal;
  ANA and RF negative;
  throat and blood cultures negative.

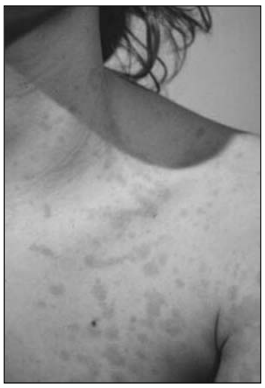
Question:

- The most likely diagnosis is?
  A. Lymphoma
  B. Adult Still's Disease
  C. Acute Rheumatic Fever
  D. Cryoglobulinemia
  E. Kikuchi's Disease

Adult Still's Disease (Systemic Onset JRA):

- Inflammatory disorder with daily fevers, arthritis and evanescent rash.
- No specific test or combination of tests.
- Yamaguchi Criteria: (5 features with 2 being major)
  Major: Fever of at least 39C for ≥week.
  Arthralgias or arthritis ≥2 weeks.
  Nonpruritic macular or mac-pap rash over trunk or extremities during febrile episodes.
  Leukocytosis ≥10K with at least 80% granulocytes.
  Minor: Sore throat; lymphadenopathy; big liver or spleen; abnormal AST, ALT, LDH; negative ANA and RF.

Adult Still's:



- Buzz words and associations:
  evanescent,
  salmon-colored rash

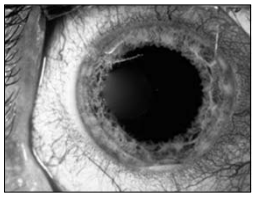
Other clues:

high ferritin; leukocytosis; arthritis; big spleen; nodes; sore throat; Koebner phenomenon = rash elicited by stroking skin or areas of pressure.

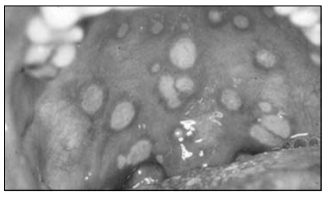
Case # 3:

- A 24-year-old man is referred from the ER where he was seen yesterday for ulcers of the mouth and penis. Three months ago he came to the U.S. from Japan to attend graduate school. He has a history of intermittent, painful oral ulcers for 3-4 years. Four days ago he developed a painful ulcer on the penile shaft. He had a similar lesion 2 months earlier. He takes no medicines and denies sexual contact for the past 5 years.

Case # 3:



- Exam: afebrile.
  Left eye is inflamed and there is a hypopyon.
  Numerous ulcers on the oral mucosa.
  No adenopathy. There is a 0.5cm ulcer on the penis. A 6mm papulo-pustular lesion is present in the right antecubital fossa; the patient says that is where they drew blood yesterday in the ER.
- Rest of the exam is normal.
- Labs: Hb 12.1; WBC 13,750.



Question :

- The most likely diagnosis is?
  A. Syphilis
  B. Behçet's disease
  C. Herpes simplex virus infection
  D. Sarcoidosis
  E. Cytomegalovirus infection

Alternate question:

- Which one of the following treatments is most likely to be beneficial in this patient?
  A. Colchicine
  B. Valacyclovir
  C. Valganciclovir
  D. Penicillin
  E. Ibuprofen

  Agents useful in Behçet's include: colchicine, dapsone, corticosteroids, thalidomide, immunosuppressive agents.

Behçet's disease:

- Multisystem inflammatory disease:
  recurrent aphthous oral ulcers and
  at least 2 of the following-
  recurrent genital ulcers, eye or skin lesions, or pathergy (red papule or pustule >5mm, 24-48 hours after skin prick by needle).
- Particularly prevalent in people of Asian or Eastern Mediterranean descent.
- Also may have GI disease (nausea, abdo. pain or diarrhea) and CNS disease (aseptic meningitis).

Behçet's disease:

- Buzz words and associations:
  ulcers in/on both mouth and genitals

  ulcers and GI symptoms
  ulcers and aseptic meningitis
  ulcers and eye problems

  Asian or Mediterranean; pathergy

Case # 4:

- A 33-year-old recent immigrant from Central America is seen for a chronic ulcer of the leg.
- The ulcer has been present for 3 months. It began after he bumped his leg on a table. Several courses of oral antibiotics have been given with no response. For the past year he has been troubled by an "upset stomach" = intermittent abdominal cramps, frequent diarrhea; and, on 2 occasions, blood in the stool. He has also had intermittent fever, sometimes accompanying diarrhea, sometimes not.

Case # 4:

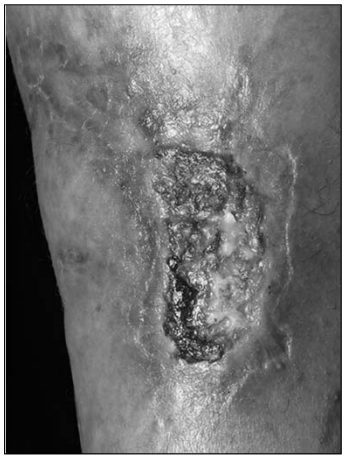
- Exam:

  T 100.2; skin lesion on leg (see image)
  Slight, diffuse abdominal tenderness.
  Otherwise unremarkable.

- Labs:

  Hb 12.4; WBC 11,150; UA normal;
  basic metabolic panel normal;
  Chest x-ray normal.

Case # 4 – leg lesion:



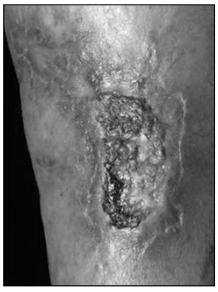
Painful and irregularly shaped ulcer with undermined borders

Question:

- Which one of the following is the most likely diagnosis?
  - A. Ulcerative colitis
  - B. Crohn's Disease
  - C. Amebic colitis
  - D. Necrotizing fasciitis
  - E. Cutaneous leishmaniasis

Pyoderma gangrenosum:

- Skin lesion associated with ulcerative colitis (Crohn's too; more common with UC, 5%).
- Lesion doesn't parallel IBD activity half the time.
- Most often on legs, but anywhere.
- Often preceded by trauma.



Painful and irregularly shaped ulcer with undermined borders

Inflammatory Bowel Disease:
(ulcerative colitis and Crohn's)

- Buzz words and associations:
  - abdo. pain/diarrhea and skin ulcer
  - abdo. pain/diarrhea and erythema nodosum
  - abdo. pain/diarrhea and back pain or stiffness
  - diarrhea for more than few weeks

Case # 5:

- A 79-year-old woman is seen for 3 weeks of fever and fatigue. Except for a history of hypertension, she has had no medical problems. Has noted jaw discomfort when chewing food, and 1 week ago had a brief episode of double vision. One week before she became ill she attended a wedding at which she ate pork from a pig that was roasted over an open fire.

Case # 5:

- Exam:
  T 102.2, P 104 reg, BP 124/84
  Slight tenderness over left scalp;
  mitral regurgitant murmur;
  rest of exam normal.
- Labs:
  Hb 13.8; WBC 9800 with normal differential; UA normal; basic metabolic panel normal; sedimentation rate 74.

Question:

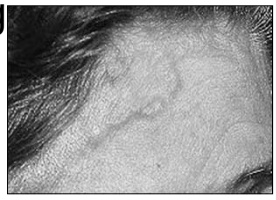
- Pending further studies, the most appropriate treatment for this patient is which one of the following?
  - A. No treatment
  - B. Heparin
  - C. Penicillin
  - D. Albendazole
  - E. Prednisone

Temporal arteritis:

- Giant cell arteritis = granulomatous vasculitis of extracranial branches of the carotid.
- Manifestations include:
  fever, headache, jaw or tongue claudication, scalp tenderness, fatigue, diplopia and high sedimentation rate.
- Immediate steroid therapy indicated to prevent blindness (won't affect biopsy yield for up to two weeks).

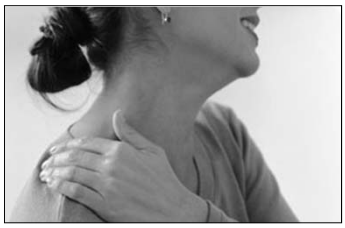
Temporal arteritis:

- Buzz words and associations:
  Elderly person with fever and:
  scalp tenderness
  diplopia or transient visual loss
  jaw or tongue fatigue or pain while eating
  high sedimentation rate

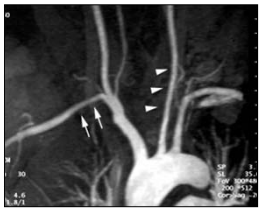


Polymyalgia rheumatica:

- Another large vessel vasculitis.
- Buzz words and associations:
  elderly person with fever, anemia, high sedimentation rate and aching and morning stiffness in proximal muscles of shoulder and hip girdle (may see associated with temporal arteritis or alone).



Takayasu's arteritis:



- Granulomatous vasculitis of aorta, its main branches and pulmonary arteries.
- Buzz words and associations:
  Young woman with fever, weight loss, sweats, arthralgias and myalgias who has: extremity claudication; visual changes; TIAs, stroke with: asymmetrical blood pressure; tenderness over carotids; diminished pulses.
- Dx: arteriography Rx: steroids

Case # 6:

- A 37-year-old man is seen for fever and hypotension. For the past 3 months he has been receiving treatment for disseminated tuberculosis. He has been feeling weak, anorectic and tired, but generally has been doing well. Three days ago he underwent emergency open reduction and fixation for a fracture of his leg sustained in a car accident. The night of surgery he developed fever and was given broad spectrum antibiotics. By the next morning he was hypotensive and had abdominal pain. He is now on pressors.

Case # 6:

- Exam:

  T 101.2; Pulse 112; BP 86/58
  Slight, diffuse abdominal tenderness.
  Otherwise unremarkable.

- Labs:

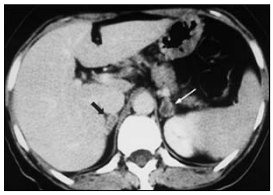
  Hb 12.4; WBC 11,150 (66% segs, 30% lymphocytes, 4% eosinophils); UA normal;
  Na 129, K 5.6; creatinine 1.8.
  Chest x-ray normal. Blood cultures negative.

Question:

- The cause of fever and hypotension in this patient will be most likely established by which one of the following?

  A. Abdominal CT scan
  B. Echocardiogram
  C. Fungal blood cultures
  D. Cosyntropin test
  E. Stopping TB medications

Adrenal crisis:



- Buzz words and associations:
  picture of septic shock in someone who has had recent stress (surgery) and a reason to have underlying adrenal insufficiency such as steroid treatment in the past year or a granulomatous infection that can involve adrenals (TB, histo.).
- Hypotension, fever, abdominal pain, nausea, hyponatremia, hyperkalemia.

Case # 7:

- A 19-year-old recent immigrant from Turkey is hospitalized for fever and severe abdominal pain that began abruptly the same day. He says he has had similar episodes on at least 3 previous occasions over the past 7 years. At the first episode he underwent appendectomy; the removed appendix was normal. Other episodes resolved spontaneously after 2-3 days.

Case # 7:

- Exam:

  T 102.2; pulse 114; no rash
  Abdominal exam: guarding, rebound tenderness, hypoactive bowel sounds.
- Labs:

  Hb 12.4; WBC 16,650; UA normal;
  basic metabolic panel normal;
  no occult blood in stool;
  CT of abdomen and pelvis normal.

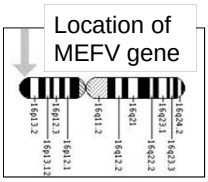
Question:

- The most likely diagnosis is:
  A. Hereditary angioneurotic edema
  B. Familial Mediterranean fever
  C. Systemic lupus erythematosus
  D. Crohn's disease
  E. Acute intermittent porphyria

Alternate question:

- This patient's condition would be most likely to respond to which one of the following treatments?
  A. Colchicine
  B. Antihistamine
  C. Methotrexate
  D. Infliximab
  E. Antimalarial

Familial Mediterranean Fever:



- Autosomal recessive disorder with sporadic, paroxysmal attacks of fever and serositis =
  (peritonitis, pleuritis, arthritis less often).
  Dx: gene testing Rx: colchicine
- Buzz words and associations:
  recurrent episodes of fever with abdominal or pleuritic pain in certain ethnic groups:
  Armenians, Turks, Sephardic Jews, N. Africans, Arabs, Greeks, Italians, Ashkenazi Jews in U.S.

Case # 8:

- A 26-year-old woman is seen for fever and cervical adenopathy. She was completely well until 9 days ago when she had the acute onset of fever and vague neck discomfort. She had no sore throat and no dental or scalp problems. Her physician found prominent anterior and posterior adenopathy. She had leukopenia and atypical lymphocytosis; the doctor suspected mononucleosis. A Monospot test was negative, and he recommended lymph node biopsy. When the results were obtained, he referred the patient to you.

Case # 8:

- Exam:

  T 101.4; unilateral anterior and posterior cervical adenopathy:
  nodes 1.5-2cm, mobile, firm, and smooth.
  Otherwise unremarkable.

- Labs:

  Hb 13.9; WBC 4,900 (9% atypical lymphocytes); Basic metabolic panel normal; Chest x-ray normal; Sed. rate 72.

Case # 8:

- Serologic studies:
  EBV consistent with old infection; CMV, Toxoplasma, Bartonella all negative. RF, ANA and anti-double stranded DNA all negative.
- Biopsy:
  architecture preserved; necrotizing lymphadenitis with histiocytic infiltrate and phagocytosed debris. No hematoxylin bodies. Stains for AFB and fungi negative.

Question:

- Which one of the following is the most likely diagnosis?
  A. Cat Scratch Disease
  B. Adult Still's Disease
  C. Sarcoidosis
  D. Kikuchi's Disease
  E. Non-Hodgkin Lymphoma

Kikuchi's Disease:

- Condition of unknown cause;
  benign; young adults (mostly women); characterized by fever and cervical adenopathy (especially posterior, usually unilateral).
- May also see arthritis, aseptic meningitis, hepato-splenomegaly, rash, uveitis.
- Most have normal CBC, but often leukopenic and atypical lymphocytes.

Kikuchi's Disease:

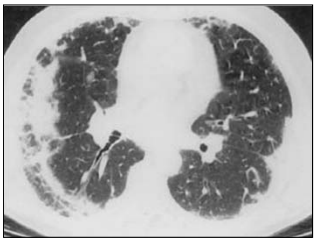
- Diagnosis by lymph node biopsy:
  preserved architecture with necrotizing histiocytic infiltrate (not neutrophils) and fragments of nuclear debris.
- Buzz words and associations:
  Acute onset fever and posterior adenopathy in young healthy woman; necrotizing adenitis with debris.

Case # 9:

- A 41-year-old woman is seen for fever, worsening respiratory symptoms, an abnormal chest x-ray, and a rash.
- She has long-standing asthma. She uses an inhaler several times a day and was recently placed on a leukotriene receptor antagonist. She is being tapered off steroids which she has taken for several months.

Case # 9:

- Exam: Temp 101.5; RR 24; diffuse wheezing; palpable purpura with subcutaneous nodules on elbows and legs.
- Labs: WBC 15,230 with 22% eosinophils.
- Chest x-ray: bilateral patchy infiltrates.
- CT scan: bilateral peripheral infiltrates.
- Skin nodule Bx: granulomas



Question:

- Which one of the following is the most likely diagnosis?
  A. Strongyloidiasis
  B. Disseminated histoplasmosis
  C. Sarcoidosis
  D. Allergic bronchopulmonary aspergillosis.
  E. Churg-Strauss syndrome

Churg-Strauss Syndrome:

- Multisystem, small vessel vasculitis with allergic rhinitis, asthma, peripheral and lung eosinophilia. Most often involves lung then skin, but can involve heart, GI tract, and nervous system.
- Presence of blood eosinophilia and pulmonary infiltrates in setting of asthma, the use of leukotriene receptor antagonist, and tapering of steroids are typical. May be p-ANCA positive.

Churg-Strauss Syndrome:

- Buzz words and associations:

  longstanding asthma with new infiltrates and eosinophilia as steroids being tapered.

  especially if also have rash (granulomas), or GI or neuropathy.

Case # 10:

- A 38-year-old man is seen for a 6-week history of cough accompanied by intermittent fever and night sweats. He has had nasal stuffiness for 4-5 months with occasional epistaxis. He lives in Philadelphia and 6 months ago traveled to Cincinnati, OH on business. He has no pets and takes no medications.

Case # 10:

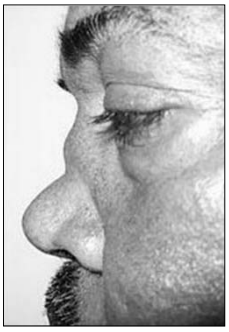
- Exam:

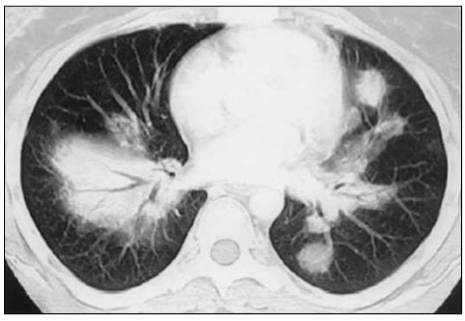
  T 100.2; RR 15; saddle nose deformity and perforation of nasal septum; lungs clear; rest of exam normal.

- Labs:

  Hb 13.8; WBC 6,900 with normal differential; UA +2 protein; basic metabolic panel normal;
  Chest x-ray: bilateral infiltrates;
  Chest CT: bilateral nodules with cavitation.

Case # 10:





Question:

- The diagnosis will most likely be supported by which one of the following?
  - A. c-ANCA
  - B. p-ANCA
  - C. Histoplasma urine antigen
  - D. Angiotensin converting enzyme (ACE)
  - E. Pulmonary angiogram

Wegener's granulomatosis:

- Systemic vasculitis of medium and small arteries.
- Primarily involves the upper and lower respiratory tracts and kidneys. Limited to upper respiratory tract or lungs in 25%. Those with limited disease are younger and more often women.
- May also involve joints, eyes, skin, and nervous system.

Wegener's:

- Dx:
  Clinical picture and antineutrophil cytoplasmic antibody (ANCA) plus biopsy.
  IFA: c-ANCA.
  ELISA: anti-proteinase 3 (PR3-ANCA) or anti-myeloperoxidase (MPO-ANCA).
- Buzz words and associations:
  Nasal symptoms and lung symptoms.
  Nasal symptoms and chest CT nodules.
  Cavitary nodules and negative blood cultures.
  Respiratory symptoms and abnormal UA.
  Saddle nose.

Case # 11:

- A 31-year-old woman seen in the ER for fever and lymphadenopathy of 3 days duration. She has a remote history of IV drug use and one month ago was started on carbamazepine (Tegretol®) after an evaluation for a new onset seizure for which no specific etiology was found.

Case # 11:

- Exam: Temp 103F; P 122; BP 98/70. Cervical and axillary adenopathy, slightly tender. Rest of exam unremarkable.
- Labs: WBC 11,450, slight increase in neutrophils. UA normal; creatinine 1.0. ALT 410; AST 230; alkaline p'tase 350. Drug screen negative.
- She was admitted to hospital.

Case # 11:

- In hospital: blood cultures negative; chest x-ray negative; HIV test negative; EBV and CMV serologies = past infection.
- On hospital day 2 she developed a patchy, erythematous, macular rash on her face and arms with periorbital edema.
  Her WBC was increased to 14,900 with increased neutrophils and no eosinophils.
  Her LFTs continued to rise.

Question:

- Which one of the following would be the most appropriate next step?
  - A. Start broad spectrum antibiotics
  - B. Start corticosteroids
  - C. Discontinue carbamazepine
  - D. Change carbamazepine to phenytoin
  - E. Start NSAIDS

Anticonvulsant Hypersensitivity Syndrome:

- Uncommon but potentially fatal.
- Due to certain anticonvulsants that break down into arene oxide metabolites:
  - Carbamazepine
  - Oxcarbazepine
  - Phenytoin
  - Primidone
  - Phenobarbital

Anticonvulsant Hypersensitivity Syndrome:

Sign/symptom	%
Fever	90-100
Rash	90
Adenopathy	70
Multiorgan effects: nephritis, encephalitis, vasculitis, ARDS, myocarditis	60
Hepatitis	50-60
Facial/periorbital edema	25
Arthralgias, myalgias	20
Eosinophilia	20

Anticonvulsant Hypersensitivity Syndrome:

- Clinical diagnosis
- Usually seen 2-4 weeks after drug begun
- Cross reaction with other aromatic benzene ring anticonvulsants = 50-80%
- Stop the drug and never give again
- Buzz words and associations:
  - Rash, hepatitis, lymphadenopathy in person on associated anticonvulsant.

Some other conditions:

- Hyperthyroidism
- Ankylosing spondylitis
- Systemic lupus
- Antiphospholipid syndrome
- Atrial myxoma
- Sweet's syndrome
- Bronchiolitis obliterans
- Lymphoma
- Thrombotic thrombocytopenic purpura